a greater number of synchronous lesions than the VATS group (12% vs 7%, respectively). To explore further, we also performed a separate analysis with synchronous primary tumors excluded and found the same pattern of recurrence. We hypothesized that if VATS missed synchronous primary tumors at the time of initial lobectomy, then the VATS group should demonstrate a greater number of metachronous tumors over time. Surprisingly, the number of metachronous lesions that developed in each group was similar. Interestingly, the influence of synchronous primary tumors as a potential confounder on outcome has not been addressed in the vast majority of published VATS studies. Based on the results of this study, the influence does not appear to be substantial because the presence of synchronous primary tumors in the multivariate model was not significant (odds ratio, 1.3; $P = .3$).

The role of histology in non–small cell lung cancer has been studied extensively. The vast majority of recent studies demonstrate that cancer recurrences and cancer-related deaths are somewhat greater in patients with adenocarcinoma than other non–small cell histologies.[19,20] The VATS group in our study demonstrated a greater number of patients with adenocarcinoma and a lower number of patients with carcinoid tumor, which would appear to favor the thoracotomy group. However, the results demonstrated the contrary.

A major limitation of this study is selection bias. The comparisons in this study are inextricably confounded by the individual surgeon's practice: 100% of the VATS lobectomies are performed by 8 surgeons, whereas 2 surgeons only perform thoracotomies. Thus unrecorded biases cannot be separated from those related to the specific technique. Surgeon bias might have led to more synchronous primary tumors in the thoracotomy group and more adenocarcinomas in the VATS group. The 2-month difference in length of follow-up could result in a slight bias in favor of the VATS group. There appears to be an immeasurable factor or selection bias that consistently leads to improved outcome in patients undergoing VATS observed with many studies, or there might be a potential biological explanation related to less trauma translating into an advantage.[21]

Thoracotomy is accepted as the gold standard in lung cancer surgery. The pattern of recurrence demonstrated in this study supports the argument that VATS lobectomy is at least equivalent to the gold standard. However, no study can replace clinical judgment at the time of the operation. In situations in which oncologic principles might be compromised, VATS should be converted to a thoracotomy. However, in appropriately selected patients VATS lobectomy is an oncologically sound procedure.

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Discussion

Dr Scott Swanson (*Boston, Mass*). Raja, you and your colleagues are to be congratulated for a very nice study looking at an important issue in lung cancer: that of recurrence following resection for early-stage disease. Your manuscript, which you kindly provided me, is well written.

You and your colleagues had excellent outcomes with an extremely low operative mortality and a local recurrence rate of about 5%, which is similar to our published recurrence rate of about 3%. Again, similar to your other papers for early clinical stage disease was a finding of about 1/3 of patients being clinically understaged, which reminds us all of the relatively low sensitivity of our radiologic imaging, even with the advent of expensive and relatively routine positron emission tomography scans. Also, you had about 10% of patients with stage IIIA or IIIB disease. First question, can you tell us how many patients had cervical mediastinoscopy?

Dr Flores. I don't know how many patients had cervical mediastinoscopy.

Dr Swanson. Did any of the patients have that before their lobectomy?

Dr Flores. If the positron emission tomography scan is positive, the practice varies among surgeons. Some will do mediastinoscopy, some will send the patients for induction chemotherapy, and some will just resect and give chemotherapy afterward.

Dr Swanson. But of these 1100 clinical stage IA, did some have a preresectional mediastinoscopy?

Dr Flores. I'm sure some. I think the number is relatively small. This was all for clinical stage IA disease, so I'd have to say the number is very, very small.

Dr Swanson. Okay. In the manuscript, you report that your data was kept in a prospectively maintained database. Can you tell us how this is prospectively maintained, what percentage of your patients had follow-up, and do you use the Society of Thoracic Surgeons database?

Dr Flores. We are members of the Society of Thoracic Surgeons database. This is prospectively maintained. Every Friday morning, we have a conference where the attending is present, we go over the staging, the attending gives their input as to what was identified at the time of surgery, and this is recorded by a single research assistant.

Dr Swanson. A number of patients were found to have synchronous primaries—about 10%. Were these suspected based on the preoperative computed tomography or were they complete surprises?

Dr Flores. That's a difficult question to answer. I think it's a very good question and something that I tried to look into. From the database, it's difficult to tell how many of these were planned and how many of these were incidentally found. The majority of them were less than a centimeter. Most likely they were incidentally found. I can't ascertain that from the database.

Dr Swanson. Finally, most striking about this paper is the statistically significant decrease in overall recurrence for video-assisted thoracoscopic surgery (VATS) versus open lobectomy, particularly because the stage distribution was the same and, more importantly, the size was identical between the 2 groups—2.1 cm—and there were more adenocarcinomas in the VATS group. This mirrors the findings of a large meta-analysis by the Minnesota group that I was involved with and published in the *Annals of Thoracic Surgery* last year. What do you make of this, and do you think this is related to the concept of less operative trauma and suppression of the immune system? With such a striking result, about a 6% difference, which would buy somebody adjuvant chemotherapy, do you think patients should be recommended to have a VATS procedure for oncologic reasons?

Excellent work, Raja, and I appreciated the chance to comment on the paper.

Dr Flores. Thank you.

I think whenever it comes to recommending a surgical procedure because of biologic reasons, and many have published on that, about decreased cytokines, interleukins, that could have a favorable oncologic outcome on the patient, I think we have to be careful about jumping to conclusions with that. I am still not convinced based on the nature of this study that there is not a selection bias going on, which is immeasurable. We did not anticipate having a higher number of synchronous primaries in the thoracotomy group. Of course, after further investigation, we identified that. That is also something that I think many of the previous VATS papers don't comment on. So I'm sure that there is some selection bias taking place that favors the VATS patients. I just can't figure it out. I hope there is a potential to figure out some underlying biologic advantage from less trauma, but I don't think I would make that statement based on this data.

Dr Bryan Meyers (*St. Louis, Mo*). You can eliminate the possibility of a selection bias by doing some sort of a propensity matching. That might be a help. You can also discuss briefly the possibility of a detection bias; if only 2 surgeons were doing the thoracotomy and 8 were doing the VATS, do they have a different protocol for following these patients up that might have led to a difference? And then the other thing which was interesting, kind of a coincidence, when we were quizzing Bob Timmerman at the General Thoracic Surgical Club about the low rate of recurrence after stereotactic radiation therapy, based on what we know exists if you do a lymph node dissection in N1 and N2 stations in clinical stage I lung cancer, there was a suggestion or hint that maybe the decreased hit on the immune system that stereotactic radiation therapy has helps reduce the chances of recurrence over VATS lobectomy. So, if you think VATS lobectomy is better because it's less invasive, then you might have to take the next step.

Dr Flores. Well, as a thoracic surgeon, I refuse to accept that. I think the good question is the propensity score. I investigated whether we should do propensity score analysis on this paper or not. We did it on our last paper. I think when you have a cohort that is as well balanced as this, it may actually make it worse, and it did make it worse on our last paper. Propensity score analyses are best when it's performed on thousands of patients. When you have hundreds of patients, such as this, I can argue that it may not be as good, and it throws out a lot of useful data when you narrow down your cohort to that extent.

Dr Mark Krasna (*Baltimore, Md*). Great paper, Raja. Because you have such a very good cohort in the 7-year time frame, you have another unique opportunity related to what Dr Meyers hinted to, and that is follow-up. So, can you tell us what the current routine follow-up is at Sloan for your patients during that 7-year period? One of the very interesting things that you found was no specific difference in your metachronous lesions. You did talk about a difference in distant failure, but it would actually be very interesting to see was there a difference in terms of the metachronous lesions with VATS lobe versus open. So did you follow the same follow-up routine for all 8 surgeons over the 7 years?

Dr Flores. All surgeons follow-up patients the same way. I'm sorry, Bryan, I forgot to address that.

Dr Krasna. So what is that algorithm?

Dr Flores. Basically, computerized axial tomography scans after surgery every 6 months.

Dr Krasna. For how many years?

Dr Flores. I follow my patients forever. I think most of the attendings will get computerized axial tomography scans once a year. It's every 6 months, and then when you hit 5 years, once a year.

Dr Cerfolio. You follow every patient forever? God bless you.

Dr Thomas D'Amico (*Durham, NC*). Raja, you explained that there were 8 surgeons that did VATS, 2 that didn't, and yet less than 50% of the total clinical stage IA were VATS. You would have thought it would be 80%. So there had to be some selection. How did it get to be less than 50%? That's the first question. And how did you analyze your conversions?

Dr Flores. Well, the majority of surgeons who do the bulk of the cases, the VATS cases and the open cases, have bigger practices than the younger guys who are just starting, so that's where the majority of cases come from. As far as conversions, this is something that I have labored over with this study, and that's a point that I always bring up, and in our last paper that was one of the center points: What do you do with the conversions. In my last paper, because survival was the primary endpoint, I included them in an intent-to-treat analysis in the VATS group. In this study recurrence rate is the primary endpoint. I included those in the thoracotomy group for a variety of reasons, including consultation with 6 biostatisticians to be sure that that was appropriate for this study. So that's usually my question. For this study, because the gold standard is thoracotomy and because of the lack of bimanual palpation in the VATS group, we thought that it was better to analyze this group in the thoracotomy group.

Dr Sandro Mattioli (*Bologna, Italy*). First, what kind of thoracotomy did you do? Second, did you consider the position of the small nodule?

Dr Flores. We looked at the location of the nodule, you know, in the upper, lower, middle lobe. We didn't look specifically within that lobe. The thoracotomy was usually a serratus-sparing thoracotomy, fifth interspace, and a Finochietto retractor was used in the majority of cases.

Dr Joseph Shrager (*Stanford, Calif*). You didn't emphasize it in your presentation, but in the abstract you emphasized that the synchronous primary rate would be much higher at thoracotomy. However, I would argue that that's basically not relevant because presumably the patients that have a suspected synchronous primary, a little 5-mm ground-glass opacity or something, on the preoperative scan, are most often going to get a thoracotomy, unless it's clearly accessible to VATS—very peripheral.

Dr Flores. I'm not sure if I agree with that. I've tried to figure out how to explain this, and there is no way of knowing ahead of time. When you look at Cerfolio's paper, and that actually prompted me to perform this, the number of malignancies that he described in his paper was 8.4%. Ours is 7%. Our thoracotomy group was 11%. I think it's tough to tell what we're doing before we get to the operating room based on what's recorded in the database.

Dr Shrager. I suspect that most people who do these operations both ways will tend to do an open operation if, in terms of second lesions, there's anything more than one very peripheral one.

Dr Flores. Not me. If there are 2 lesions there, I'll go ahead with the lobectomy for the larger lesion and I'll wedge or segment out the second lesion.

Dr Shrager. You can't always find a 5-mm ground-glass lesion with your finger at VATS—unless it's very peripheral.

Dr Flores. Most of the time with digital palpation, I'll argue that we can.